	Type	L #	Hits	Search Text	DBs
1	BRS	L1	66	(perfusing or perfuse or treat or treating or expose or exposing) near8 cell same microfluidic	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB
2	BRS	L2	49	L1 and (retain or retained or retaining or trap or trapping or trapped or hold or held or immoblize or immobilized) near8 cell	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB
3	BRS	L3	12	L2 and (retention or retained) near8 cell	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB

	Type	L #	Hits	Search Text	DBs
4	BRS	L4	17	2 and (egg or embryo)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB
5	BRS	L5	19	1 and (egg or embryo)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB
6	BRS	L6	5	3 and (egg or embryo)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB

	Type	L #	Hits	Search Text	DBs
7	BRS	L7	20014	microfluid$6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB
8	BRS	L8	5490	7 and cell$5 near8 (growth or culture)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB
9	BRS	L9	50	7 and in near6 vitro near8 fertiliz$8	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB

	Type	L #	Hits	Search Text	DBs
10	BRS	L10	38	2 and cell$5 near8 (growth or culture)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB
11	BRS	L11	31	2 and cell$5 near8 (growth or culture) same (drug or medium or reagent or hormone or agent)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB
12	BRS	L12	4205	7 and cell$5 near8 (growth or culture) same (drug or medium or reagent or hormone or agent)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB

	Type	L #	Hits	Search Text	DBs
13	BRS	L13	4205	8 and cell$5 near8 (growth or culture) same (drug or medium or reagent or hormone or agent)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB
14	BRS	L14	1436	12 and (retain or retained or retaining or trap or trapping or trapped or hold or held or immoblize or immobilized) near8 cell	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB
15	BRS	L15	1436	13 and (retain or retained or retaining or trap or trapping or trapped or hold or held or immoblize or immobilized) near8 cell	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB

	Type	L #	Hits	Search Text	DBs
16	BRS	L16	277	14 and (chamber or well or receptacle or channel or microchannel or vessel or container) same (valve or microvalve)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB
17	BRS	L17	277	15 and (chamber or well or receptacle or channel or microchannel or vessel or container) same (valve or microvalve)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB
18	BRS	L18	131	16 and (elastomer$6 or pdms or polydimethylsiloxane)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB

	Type	L #	Hits	Search Text	DBs
19	BRS	L19	51	16 and elastomer$6 with (pdms or polydimethylsiloxane)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB
20	BRS	L20	51	17 and elastomer$6 with (pdms or polydimethylsiloxane)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB

	Type	L #	Hits	Search Text	DBs
1	BRS	L1	66	(perfusing or perfuse or treat or treating or expose or exposing) near8 cell same microfluidic	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB
2	BRS	L2	49	L1 and (retain or retained or retaining or trap or trapping or trapped or hold or held or immoblize or immobilized) near8 cell	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB
3	BRS	L3	12	L2 and (retention or retained) near8 cell	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB

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NEWS 5	AUG 20	CA/CAplus enhanced with CAS indexing in pre-1907 records
NEWS 6	AUG 27	Full-text patent databases enhanced with predefined patent family display formats from INPADOCDB
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NEWS 16	OCT 19	BEILSTEIN updated with new compounds
NEWS 17	NOV 15	Derwent Indian patent publication number format enhanced
NEWS 18	NOV 19	WPIX enhanced with XML display format
NEWS 19	NOV 30	ICSD reloaded with enhancements
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NEWS 21	DEC 14	BEILSTEIN pricing structure to change
NEWS 22	DEC 17	USPATOLD added to additional database clusters
NEWS 23	DEC 17	IMSDRUGCONF removed from database clusters and STN
NEWS 24	DEC 17	DGENE now includes more than 10 million sequences
NEWS 25	DEC 17	TOXCENTER enhanced with 2008 MeSH vocabulary in MEDLINE segment
NEWS 26	DEC 17	MEDLINE and LMEDLINE updated with 2008 MeSH vocabulary
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NEWS EXPRESS 19 SEPTEMBER 2007: CURRENT WINDOWS VERSION IS V8.2, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 SEPTEMBER 2007.

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=> s microfluid?
L1       24541 MICROFLUID?

=> s (perfus? or expos? or treat? or  saturat? or diffus?) (8w) cell?
L2      209425 (PERFUS? OR EXPOS? OR TREAT? OR SATURAT? OR DIFFUS?) (8W) CELL?

=> s (immobiliz? or hold? or retain? or trap? or held) (8w) cell?
L3       48510 (IMMOBILIZ? OR HOLD? OR RETAIN? OR TRAP? OR HELD) (8W) CELL?

=> s l1 same l2 same l3
MISSING OPERATOR L1 SAME
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l1 (p) l2 (p) l3
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L2 (P) L6'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L6 (P) L10'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L3 (P) L7'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L7 (P) L11'
L4          33 L1 (P) L2 (P) L3

=> dup remove l4 1-33
'1-33' IS NOT VALID.  VALID FILE NAMES ARE 'CAPLUS, COMPENDEX, INSPEC'
You have entered a file name of duplicates to keep that is not
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'1-33' IS NOT VALID. VALID FILE NAMES ARE 'CAPLUS, COMPENDEX, INSPEC'
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The file names of duplicates that can be kept are listed above.
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ENTER FILE NAMES OF DUPLICATES TO KEEP:caplus
PROCESSING COMPLETED FOR L4
L5 22 DUPLICATE REMOVE L4 CAPLUS (11 DUPLICATES REMOVED)

=> display l5 1-22 ibib abs

L5 ANSWER 1 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:733811 CAPLUS
DOCUMENT NUMBER: 147:67099
TITLE: Method and apparatus for integrated single cell handling, electroporation and electrofusion for use in diagnosis and drug screening
INVENTOR(S): Lee, Luke P.; Seo, Jeonggi; Ionescu-Zanetti, Cristian; Khine, Michelle; Lau, Adrian
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: U.S. Pat. Appl. Publ., 31pp., Cont.-in-part of Appl. No. PCT/US05/008349.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2007155016	A1	20070705	US 2006-466104	20060821
WO 2005089253	A2	20050929	WO 2005-US8349	20050314
WO 2005089253	A3	20070315		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

US 2004-552892P	P	20040312
WO 2005-US8349	A2	20050314
US 2005-710305P	P	20050821

AB The present invention provides a method and systems for improved cell handling in microfluidic systems and devices using lateral cell trapping and methods of fabrication of the same that allow for selective low voltage electroporation and electrofusion. The invention accomplishes successful single cell electroporation by generally both isolating the cell and providing a well focused elec. field through the device configuration. In specific embodiments, a device according to the invention can selectively trap targeted cells and focus an elec. field for reversible electroporation (in which the pores reseal), intracellular perfusion, and/or cell fusion. Specific embodiments involve lateral cell trapping junctions at a micron scale, integrated with microfluidic channels wherein cell

immobilization or trapping pores generally are arranged as openings in a sidewall or analogous structure of a main fluidic channel. This cell trapping structure is referred to as a lateral pore or junction. In specific embodiments, microfabricated devices can be ideally suited to both isolate single cells and focus an elec. field for cell electroporation. A polydimethylsiloxane (PDMS)-based platform able to create a transmembrane potential across a cell using low voltages such that dielec. breakdown of the membrane is achieved. In particular embodiments, the invention applies a low voltage (<about 1 V) to create a large potential drop (of about 750 V/cm) across the cell membrane. In response to this transmembrane potential, dielec. breakdown of the membrane is achieved and cell membrane phospholipids can rearrange to create transient pores. These pores allow compds. to be delivered into the cell, for example via an integrated capillary channels or a backside perfusion channel. In alternative embodiments, cells can also be fused with each other or with preloaded vesicles for volume controlled intracellular delivery using electrofusion.

L5 ANSWER 2 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2007:196908 CAPLUS
DOCUMENT NUMBER: 146:311797
TITLE: Noninvasive Acoustic Cell Trapping in a Microfluidic Perfusion System for Online Bioassays
AUTHOR(S): Evander, Mikael; Johansson, Linda; Lilliehorn, Tobias; Piskur, Jure; Lindvall, Magnus; Johansson, Stefan; Almqvist, Monica; Laurell, Thomas; Nilsson, Johan
CORPORATE SOURCE: Department of Electrical Measurements Department of Cell and Organism Biology and Department of Child and Adolescent Psychiatry, Lund University, Lund, Swed.
SOURCE: Analytical Chemistry (Washington, DC, United States) (2007), 79(7), 2984-2991
CODEN: ANCHAM; ISSN: 0003-2700
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Techniques for manipulating, separating, and trapping particles and cells are highly desired in today's bioanal. and biomedical field. The microfluidic chip-based acoustic noncontact trapping method earlier developed within the group now provides a flexible platform for performing cell- and particle-based assays in continuous flow microsystems. An acoustic standing wave is generated in etched glass channels (600 + 61 μm2) by miniature ultrasonic transducers (550 + 550 + 200 μm3). Particles or cells passing the transducer will be retained and levitated in the center of the channel without any contact with the channel walls. The maximum trapping force was calculated to be 430±135 pN by measuring the drag force exerted on a single particle levitated in the standing wave. The temperature increase in the channel was characterized by fluorescence measurements using rhodamine B, and levels of moderate temperature increase were noted. Neural stem cells were acoustically trapped and shown to be viable after 15 min. Further evidence of the mild cell handling conditions was demonstrated as yeast cells were successfully cultured for 6 h in the acoustic trap while being perfused by the cell medium at a flowrate of 1 μL/min. The acoustic microchip method facilitates trapping of single cells as well as larger cell clusters. The noncontact mode of cell handling is especially important when studies on nonadherent cells are performed, e.g., stem cells, yeast cells, or blood cells, as mech. stress and surface interaction are minimized. The demonstrated acoustic trapping of cells and particles enables cell- or particle-based bioassays to be performed in a continuous flow format.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2007:1098755 CAPLUS
TITLE: A hybrid microsystem for parallel perfusion experiments on living cells
AUTHOR(S): Greve, Frauke; Seemann, Livia; Hierlemann, Andreas; Lichtenberg, Jan
CORPORATE SOURCE: Physical Electronics Laboratory, Zurich, 8093, Switz.
SOURCE: Journal of Micromechanics and Microengineering (2007), 17(8), 1721-1730
CODEN: JMMIEZ; ISSN: 0960-1317
PUBLISHER: Institute of Physics Publishing
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A fully integrated microchip device for performing a complete and automated sample-perfusion experiment on living cells is presented. Cells were trapped and immobilized in a defined grid pattern inside a small 0.5 μl volume incubation chamber by pneumatic anchoring on 1000 5-μm orifices. This new cell trapping technique assures a precise and repeatable cell quantity for each experiment and enables the formation of a homogeneous cell population in the incubation chamber. The microsystem includes a perforated silicon chip seamlessly integrated by a new embedding technique in a larger elastomer substrate, which features the microfluidic network. The latter forms the incubation chamber and allows for economic logarithmic dilution of the sample reagent over a range of three orders of magnitude with subsequent perfusion of the cell population. First, the logarithmic dilution stage was validated using quant. fluorescent imaging of fluorescein solution Then, the cell adhesion and culturing inside the incubation chamber was studied using primary normal human dermal fibroblasts (NHDFs). The cells adhered well on laminin-coated surfaces and proliferated to form a confluent cell layer after 6 days in vitro. Finally, the complete system was tested by a perfusion experiment with cultured NHDFs, which were exposed to a fluorescent cell tracker at dilns. of 100 μM, 10 μM, 1 μM, 0.1 μM and 0 μM at a flow rate of 1.25 μl min-1 for 20 min. Fluorescence imaging of the cell array after incubation and image anal. showed a logarithmic relationship between sample concentration and the fluorescence signal. This paper describes the fabrication of the components and the assembly of the microsystem, the design approach and the validation of the sample diluter, cell-adhesion and cell-culturing expts. over several days.

L5 ANSWER 4 OF 22 INSPEC (C) 2007 IET on STN
ACCESSION NUMBER: 2007:9329317 INSPEC
TITLE: Fabrication of a bio-MEMS based cell-chip for toxicity monitoring
AUTHOR: Jong Hyun Lee; Sung Keun Yoo; (Dept. of Mechatronics, Gwangju Inst. of Sci. & Technol., South Korea), Jin Hyung Lee; Sung-Sik Yun; Man Bock Gu
SOURCE: Biosensors & Bioelectronics (15 March 2007), vol.22, no.8, p. 1586-92, 27 refs.
CODEN: BBIOE4, ISSN: 0956-5663
SICI: 0956-5663(20070315)22:8L.1586:FMBC;1-E
Doc.No.: S0956-5663(06)00315-0
Published by: Elsevier, UK
DOCUMENT TYPE: Journal
TREATMENT CODE: Practical
COUNTRY: United Kingdom
LANGUAGE: English
AN 2007:9329317 INSPEC
AB A bio-MEMS based cell-chip that can detect a specific toxicity was

fabricated by patterning and immobilizing bioluminescent bacteria in a microfluidic chip. Since the emitted light intensity of bioluminescent bacteria changed in response to the presence of chemicals, the bacteria were used as the toxicity indicator in this study. A pattern of immobilized cells was successfully generated by photolithography, utilizing a water-soluble and negatively photosensitive polymer, PVA-SbQ (polyvinyl alcohol-styrylpyridinium) as an immobilization material. Using the recombinant Escherichia coli (E. coli) strain, GC2, which is sensitive to general toxicity, the following were investigated for the immobilization: an acceptable dose of long-wavelength UV light, the biocompatibility of the polymer, and the effect of the chip-environment. We found that 10min of UV light exposure, the toxicity of polymer (SPP-H-13-bio), and the other chip-environment did not inhibit cell metabolism significantly for making a micro-cell-chip. Detection of a specific toxicity was demonstrated by simply immobilizing the bioluminescent bacteria, DK1, which increased bioluminescence in the presence of oxidative damage in the cells. An injection of hydrogen peroxide of 0.88mM induced 10-fold increase in bioluminescent intensity confirming the capability of the chip for toxicity monitoring. [All rights reserved Elsevier]

L5 ANSWER 5 OF 22 INSPEC (C) 2007 IET on STN
ACCESSION NUMBER: 2007:9675046 INSPEC
TITLE: Development of a microfluidic device for determination of cell osmotic behavior and membrane transport properties
AUTHOR: Hsiu-hung Chen (Washington Univ., Seattle, USA), Purtteman, J.J.P. (Washington Univ., Seattle, USA), Heimfeld, S.; Folch, A.; Dayong Gao
SOURCE: Cryobiology (Dec. 2007), vol.55, no.3, p. 200-9, 40 refs.
CODEN: CRYBAS, ISSN: 0011-2240
Doc.No.: S0011-2240(07)00115-0
Published by: Academic Press, USA
DOCUMENT TYPE: Journal
TREATMENT CODE: Practical; Experimental
COUNTRY: United States
LANGUAGE: English
AN 2007:9675046 INSPEC
AB An understanding of cell osmotic behavior and membrane transport properties is indispensable for cryobiology research and development of cell-type-specific, optimal cryopreservation conditions. A microfluidic perfusion system is developed here to measure the kinetic changes of cell volume under various extracellular conditions, in order to determine cell osmotic behavior and membrane transport properties. The system is fabricated using soft lithography and is comprised of microfluidic channels and a perfusion chamber for trapping cells. During experiments, rat basophilic leukemia (RBL-1 line) cells were injected into the inlet of the device, allowed to flow downstream, and were trapped within a perfusion chamber. The fluid continues to flow to the outlet due to suction produced by a Hamilton Syringe. Two sets of experiments have been performed: the cells were perfused by (1) hypertonic solutions with different concentrations of non-permeating solutes and (2) solutions containing a permeating cryoprotective agent (CPA), dimethylsulfoxide (Me2SO), plus non-permeating solute (sodium chloride (NaCl)), respectively. From experiment (1), cell osmotically inactive volume (Vb) and the permeability coefficient of water (Lp) for RBL cells are determined to be 41% [n = 18, correlation coefficient (r2) of 0.903] of original/ isotonic volume, and 0.32 ± 0.05 μm/min/atm (n = 8, r2 > 0.963), respectively, for room temperature (22 oC). From experiment (2), the permeability coefficient of water (Lp) and of Me2SO (Ps) for RBL

cells are 0.38 ± 0.09 μm/min/atm and (0.49 ± 0.13) x 10-3 cm/min (w = 5, r2 > 0.86), respectively. We conclude that this device enables us to: (1) readily monitor the changes of extracellular conditions by perfusing single or a group of cells with prepared media; (2) confine cells (or a cell) within a monolayer chamber, which prevents imaging ambiguity, such as cells overlapping or moving out of the focus plane; (3) study individual cell osmotic response and determine cell membrane transport properties; and (4) reduce labor requirements for its disposability and ensure low manufacturing costs. [All rights reserved Elsevier].

L5 ANSWER 6 OF 22 COMPENDEX COPYRIGHT 2007 EEI on STN DUPLICATE 3
ACCESSION NUMBER: 2007(3):2745 COMPENDEX
TITLE: A microfluidic platform for 3-dimensional cell culture and cell-based assays.
AUTHOR: Kim, Minseok S. (Department of BioSystems Korea Advanced Institute of Science and Technology (KAIST), Yuseong-gu, Daejeon 305-701, South Korea); Yeon, Ju Hun; Park, Je-Kyun
SOURCE: Biomedical Microdevices v 9 n 1 February 2007 2007.p 25-34
SOURCE: Biomedical Microdevices v 9 n 1 February 2007 2007.p 25-34
CODEN: BMICFC ISSN: 1387-2176
PUBLICATION YEAR: 2007
DOCUMENT TYPE: Journal
TREATMENT CODE: Experimental
LANGUAGE: English
AN 2007(3):2745 COMPENDEX
AB This paper reports a novel microfluidic platform introducing peptide hydrogel to make biocompatible microenvironment as well as realizing in situ cell-based assays. Collagen composite, OPLA and Puramatrix scaffolds are compared to select good environment for human hepatocellular carcinoma cells (HepG2) by albumin measurement. The selected biocompatible self-assembling peptide hydrogel, Puramatrix, is hydrodynamically focused in the middle of main channel of a microfluidic device, and at the same time the cells are 3-dimensionally immobilized and encapsulated without any additional surface treatment. HepG2 cells have been 3-dimensionally cultured in a poly(dimethylsiloxane) (PDMS) microfluidic device for 4 days. The cells cultured in micro peptide scaffold are compared with those cultured by conventional petri dish in morphology and the rate of albumin secretion. By injection of different reagents into either side of the peptide scaffold, the microfluidic device also forms a linear concentration gradient profile across the peptide scaffold due to molecular diffusion. Based on this characteristic, toxicity tests are performed by Triton X-100. As the higher toxicant concentration gradient forms, the wider dead zone of cells in the peptide scaffold represents. This microfluidic platform facilitates in vivo-like 3-dimensional microenvironment, and have a potential for the applications of reliable cell-based screening and assays including cytotoxicity test, real-time cell viability monitoring, and continuous dose-response assay. $CPY Springer Science+Business Media, LLC 2006. 41 Refs.

L5 ANSWER 7 OF 22 COMPENDEX COPYRIGHT 2007 EEI on STN
ACCESSION NUMBER: 2007(48):11301 COMPENDEX
TITLE: Holographic optical tweezers combined with a microfluidic device for exposing cells to fast environmental changes.
AUTHOR: Eriksson, Emma (Department of Physics Goteborg University, SE-41296 Goteborg, Sweden); Scrimgeour,

Jan; Enger, Jonas; Goksor, Mattias
MEETING TITLE: Bioengineered and Bioinspired Systems III.
MEETING ORGANIZER: SPIE Europe
MEETING LOCATION: Maspalomas, Gran Canaria, Spain
MEETING DATE: 02 May 2007-04 May 2007
SOURCE: Proceedings of SPIE - The International Society for Optical Engineering v 6592 2007.
SOURCE: Proceedings of SPIE - The International Society for Optical Engineering v 6592 2007., arn: 65920P
SOURCE: Bioengineered and Bioinspired Systems III
CODEN: PSISDG ISSN: 0277-786X
ISBN: 0819467200; 9780819467201
PUBLICATION YEAR: 2007
MEETING NUMBER: 70583
DOCUMENT TYPE: Conference Article
TREATMENT CODE: Theoretical; Experimental
LANGUAGE: English
AN 2007(48):11301 COMPENDEX
AB Optical manipulation techniques have become an important research tool for single cell experiments in microbiology. Using optical tweezers, single cells can be trapped and held during long experiments without risk of cross contamination or compromising viability. However, it is often desirable to not only control the position of a cell, but also to control its environment. We have developed a method that combines optical tweezers with a microfluidic device. The microfluidic system is fabricated by soft lithography in which a constant flow is established by a syringe pump. In the microfluidic system multiple laminar flows of different media are combined into a single channel, where the fluid streams couple viscously. Adjacent media will mix only by diffusion, and consequently two different environments will be separated by a mixing region a few tens of micrometers wide. Thus, by moving optically trapped cells from one medium to another we are able to change the local environment of the cells in a fraction of a second. The time needed to establish a change in environment depends on several factors such as the strength of the optical traps and the steepness of the concentration gradient in the mixing region. By introducing dynamic holographic optical tweezers several cells can be trapped and analyzed simultaneously, thus shortening data acquisition time. The power of this system is demonstrated on yeast (Saccharomyces cerevisiae) subjected to osmotic stress, where the volume of the yeast cell and the spatial localization of green fluorescent proteins (GFP) are monitored using fluorescence microscopy. 28 Refs.

L5 ANSWER 8 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:400369 CAPLUS
DOCUMENT NUMBER: 144:463734
TITLE: Microfluidic chip-based analytic method for cell inclusions
INVENTOR(S): Lin, Bingcheng; Yu, Linfen; Ge, Hongwei; Shen, Zheng; Ma, Yinfa
PATENT ASSIGNEE(S): Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 13 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1734265	A	20060215	CN 2004-10021600	20040803

PRIORITY APPLN. INFO.: CN 2004-10021600 20040803

AB The title method comprises: (1) constructing a model of biotin-avidin system on the surface of a microfluidic channel after amination treatment, (2) immobilizing a biotinylated cell to a specific site of the channel surface by the interaction between the biotin and avidin, (3) lysing the cell with a buffer containing chemical reagent (0.1-0.4% sodium dodecyl sulfonate) under the drive of high voltage (100-600 V/cm), and (4) performing electrophoretic anal. of inclusions released from the cell. The method has the advantages of full contact of cell and the reagent, quick cell lysis and no need of complicated device.

L5 ANSWER 9 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 4

ACCESSION NUMBER: 2005:1291314 CAPLUS
DOCUMENT NUMBER: 144:419474
TITLE: Rapid localized cell trapping on biodegradable polymers using cell surface derivatization and microfluidic networking
AUTHOR(S): Sinclair, Jason; Salem, Aliasger K.
CORPORATE SOURCE: Division of Pharmaceutics, College of Pharmacy, University of Iowa, Iowa City, IA, 52242, USA
SOURCE: Biomaterials (2006), 27(9), 2090-2094
CODEN: BIMADU; ISSN: 0142-9612
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Spatial control over cell attachment is essential for controlling cell behavior and engineering cell-based sensor arrays. Here we report on a patterning procedure that can be utilized on a wide range of adherent and non-adherent cell types without the need to identify the exact peptide sequence or extracellular matrix (ECM) necessary for optimal cell attachment. This is achieved by converting native sialic residues present on the surface of most cells into non-native aldehydes using a mild sodium periodate treatment. The aldehyde groups are then reacted with biotin hydrazide to produce biotinylated cells. Avidin is patterned onto the surface of a biotinylated biodegradable block copolymer, polylactide-poly(ethylene glycol)-biotin (PLA-PEG-biotin) by microfluidic networking using a PDMS stamp. The biotinylated cells then bind specifically to the patterned avidin regions. The PEG that is presented from the PLA-PEG-biotin copolymer in the regions without avidin immobilization minimizes cell binding in the non-patterned regions.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 5

ACCESSION NUMBER: 2006:1127317 CAPLUS
DOCUMENT NUMBER: 146:77201
TITLE: Dynamic single cell culture array
AUTHOR(S): Di Carlo, Dino; Wu, Liz Y.; Lee, Luke P.
CORPORATE SOURCE: Berkeley Sensor and Actuator Center, Biomolecular Nanotechnology Center, Department of Bioengineering, University of California, Berkeley, CA, 94720, USA
SOURCE: Lab on a Chip (2006), 6(11), 1445-1449
CODEN: LCAHAM; ISSN: 1473-0197
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It is important to quantify the distribution of behavior among a population of individual cells to reach a more complete quant. understanding of cellular processes. Improved high-throughput anal. of single cell behavior requires uniform conditions for individual cells with controllable cell-cell interactions, including diffusible and contact

elements. Uniform cell arrays for static culture of adherent cells have previously been constructed using protein micropatterning techniques but lack the ability to control diffusible secretions. Here the authors present a microfluidic-based dynamic single cell culture array that allows both arrayed culture of individual adherent cells and dynamic control of fluid perfusion with uniform environments for individual cells. In the device no surface modification is required and cell loading is done in <30 s. The device consists of arrays of phys. U-shaped hydrodynamic trapping structures with geometries that are biased to trap only single cells. HeLa cells were shown to adhere at a similar rate in the trapping array as on a control glass substrate. Addnl., rates of cell death and division were comparable to the control experiment Approx. 100 individual isolated cells were observed growing and adhering in a field of view spanning .apprx.1 mm2 with >85% of cells maintained within the primary trapping site after 24 h. Also, >90% of the cells were adherent and only 5% had undergone apoptosis after 24 h of perfusion culture within the trapping array. The authors anticipate uses in single cell anal. of drug toxicity with physiol. relevant perfused dosages as well as investigation of cell signaling pathways and systems biol.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 11 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 6

ACCESSION NUMBER: 2006:785561 CAPLUS
DOCUMENT NUMBER: 145:391585
TITLE: Fabrication of cell-containing hydrogel microstructures inside microfluidic devices that can be used as cell-based biosensors
AUTHOR(S): Koh, Won-Gun; Pishko, Michael V.
CORPORATE SOURCE: Department of Chemical Engineering, Yonsei University, Seodaemoon-Gu, Seoul, 120-749, S. Korea
SOURCE: Analytical and Bioanalytical Chemistry (2006), 385(8), 1389-1397
CODEN: ABCNBP; ISSN: 1618-2642
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This paper describes microfluidic systems containing immobilized hydrogel-encapsulated mammalian cells that can be used as cell-based biosensors. Mammalian cells were encapsulated in three-dimensional poly(ethylene glycol) (PEG) hydrogel microstructures which were photolithog. polymerized in microfluidic devices and grown under static culture conditions. The encapsulated cells remained viable for a week and were able to carry out enzymic reactions inside the microfluidic devices. Cytotoxicity assays proved that small mol. weight toxins such as sodium azide could easily diffuse into the hydrogel microstructures and kill the encapsulated cells, which resulted in decreased viability. Furthermore, heterogeneous hydrogel microstructures encapsulating two different phenotypes in discrete spatial locations were also successfully fabricated inside microchannels.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 12 OF 22 COMPENDEX COPYRIGHT 2007 EEI on STN

ACCESSION NUMBER: 2006(1):3829 COMPENDEX
TITLE: A packed microcolumn approach to a cell-based biosensor.
AUTHOR: Flemming, Jeb H. (Sandia National Laboratories Mail Stop 1425, Albuquerque, NM 87185-1425, United States); Baca, Helen K.; Werner-Washburne, Margaret; Brozik, Susan M.; Lopez, Gabriel P.

SOURCE: Sensors and Actuators, B: Chemical v 113 n 1 Jan 17 2006 2006.p 376-381
SOURCE: Sensors and Actuators, B: Chemical v 113 n 1 Jan 17 2006 2006.p 376-381
CODEN: SABCEB ISSN: 0925-4005
PUBLICATION YEAR: 2006
DOCUMENT TYPE: Journal
TREATMENT CODE: Theoretical; Experimental
LANGUAGE: English
AN 2006(1):3829 COMPENDEX
AB We present and evaluate a new approach to cell immobilization for use in cell-based biosensors. We have fabricated a microfluidic channel using poly(dimethylsiloxane) (PDMS) with cell entrapment posts for the gentle packing and immobilization of yeast cells. This method of immobilization allows for a density of metabolically active cells greater than 8.0 * 106 cells/mm3. The packed microcolumn approach addresses simple diffusional limitations inherent in traditional suspension and membrane entrapment techniques. By utilizing genetically engineered whole cells, rather then cellular components, the sensor is capable of detecting and responding to a wide range of biologically active compounds. In this study, Saccharomyces cerevisiae was genetically engineered to produce yellow fluorescent protein (YFP) when exposed to galactose. Fluorescence response of packed cells (G 1 phase) to galactose required 40% longer than the fluorescent response of cells grown in suspension. To address concerns of long-term viability (>60 days) and cell overgrowth, stationary phase cells were also tested in the microfluidic channel. Response time required approximately 50% longer than non-stationary phase cells packed inside the microfluidic channel. Additionally, cellular response as a function of the target analyte concentration was investigated and response time versus analyte concentration is reported. This report demonstrates proof-of-concept of using protein expression-based biosensors, based upon a packed, microcolumn architecture, as a dependable long-term storage platform. $CPY 2005 Elsevier B.V. All rights reserved. 23 Refs.

L5 ANSWER 13 OF 22 INSPEC (C) 2007 IET on STN
ACCESSION NUMBER: 2007:9296596 INSPEC
TITLE: High-throughput cell-based screening system with on-chip dilution stage
AUTHOR: Greve, F.; Seemann, L.; Bonneick, S.; Lichtenberg, J.; Hierlemann, A. (Phys. Electron. Lab., Eidgenossische Tech. Hochschule, Zurich, Switzerland)
SOURCE: 2006 International Conference on Microtechnologies in Medicine and Biology (IEEE Cat. No.06EX1357), 2006, p. 4 pp. of CD-ROM pp., 2 refs.
ISBN: 1 4244 0338 3
Price: 1-4244-0338-3/06/$20.00
Published by: IEEE, Piscataway, NJ, USA
Conference: 2006 International Conference on Microtechnologies in Medicine and Biology, Okinawa, Japan, 9-12 May 2006
DOCUMENT TYPE: Conference; Conference Article
TREATMENT CODE: Practical; Experimental
COUNTRY: United States
LANGUAGE: English
AN 2007:9296596 INSPEC
AB A microchip-based approach for performing a complete and automated drug-screening assay on living cells is presented. Cells are trapped and immobilized in a small 0.5-μl-volume incubation chamber by means of orifice microstructures and are subsequently incubated with drug dilutions ranging over three orders of magnitude. The microsystem

includes a perforated silicon chip embedded in a larger elastomer substrate, which features the microfluidic network and the incubation chamber. This article describes the modeling and the fabrication of the microchip components, immobilization of normal human dermal fibroblasts (NHDFs) and a screening experiment with cultured NHDFs, which have been exposed to a fluorescent cell tracker

L5 ANSWER 14 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 2006:197194 CAPLUS
DOCUMENT NUMBER: 144:407343
TITLE: Microfluidics technology for manipulation and analysis of biological cells
AUTHOR(S): Yi, Changqing; Li, Cheuk-Wing; Ji, Shenglin; Yang, Mengsu
CORPORATE SOURCE: Department of Biology and Chemistry, City University of Hong Kong, Hong Kong, Peop. Rep. China
SOURCE: Analytica Chimica Acta (2006), 560(1-2), 1-23
CODEN: ACACAM; ISSN: 0003-2670
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Anal. of the profiles and dynamics of mol. components and sub-cellular structures in living cells using microfluidic devices has become a major branch of bioanal. chemical during the past decades. Microfluidic systems have shown unique advantages in performing anal. functions such as controlled transportation, immobilization, and manipulation of biol. mols. and cells , as well as separation, mixing, and dilution of chemical reagents, which enables the anal. of intracellular parameters and detection of cell metabolites, even on a single-cell level. This article provides an in-depth review on the applications of microfluidic devices for cell-based assays in recent years (2002-2005). Various cell manipulation methods for microfluidic applications, based on magnetic, optical, mech., and elec. principles, are described with selected examples of microfluidic devices for cell-based anal. Microfluidic devices for cell treatment, including cell lysis, cell culture, and cell electroporation, are surveyed and their unique features are introduced. Special attention is devoted to a number of microfluidic devices for cell-based assays, including micro cytometer, microfluidic chemical cytometry, biochem. sensing chip, and whole cell sensing chip.
REFERENCE COUNT: 185 THERE ARE 185 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 15 OF 22 INSPEC (C) 2007 IET on STN
ACCESSION NUMBER: 2005:8469179 INSPEC
DOCUMENT NUMBER: A2005-15-8780-020; B2005-08-2575-004
TITLE: Gentle cell trapping and release on a microfluidic chip by in situ alginate hydrogel formation
AUTHOR: Braschler, T.; Johann, R.; Heule, M.; Metref, L.; Renaud, P. (STI-LMIS, Swiss Fed. Inst. of Technol., Lausanne, Switzerland)
SOURCE: Lab on a Chip (May 2005), vol.5, no.5, p. 553-9, 26 refs.
CODEN: LCAHAM, ISSN: 1473-0197
SICI: 1473-0197(200505)5:5L.553:GCTR;1-V
Published by: R. Soc. Chem, UK
DOCUMENT TYPE: Journal

TREATMENT CODE: Practical; Experimental
COUNTRY: United Kingdom
LANGUAGE: English
AN 2005:8469179 INSPEC DN A2005-15-8780-020; B2005-08-2575-004
AB Microfluidic devices are increasingly used to perform biological experiments on a single-cell basis. However, long-term stability of cell positions is still an issue. A novel biocompatible method for cell entrapment and release on a microchip is presented. It is based on the controlled formation of an alginate hydrogel by bringing two laminar flows of alginate and calcium ions in the range of 2 mM to 40 mM into contact. The resulting growth of a gel bar is used to enclose and immobilize yeast cells. Adding ethylenediaminetetraacetic acid (EDTA) to the alginate solution allows for control of the hydrogel growth, and by varying the ratio of Ca2+ to EDTA concentrations gel growth or gel shrinkage can be induced at will. Trapped cells are released during shrinkage of the gel. The trapping efficiency for different cell speeds is investigated and the properties of gel growth are discussed using a diffusion model. Precise positioning of a single cell is demonstrated. The technique presented allows not only the reversible immobilization of cells under gentle conditions but also offers the potential of long-term cell cultures as shown by on-chip incubation of yeast cells. The procedure may provide a simple and fully biocompatible technique for a multitude of innovative experiments on cells in microsystems

L5 ANSWER 16 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:736430 CAPLUS
TITLE: Generating cell arrays inside microfluidic networks
AUTHOR(S): Forry, Sam P.; Reyes, Darwin R.; Gaitan, Michael; Locascio, Laurie E.
CORPORATE SOURCE: Analytical Chemistry Division, National Institute of Standards and Technology, Gaithersburg, MD, 20899, USA
SOURCE: Abstracts of Papers, 230th ACS National Meeting, Washington, DC, United States, Aug. 28-Sept. 1, 2005 (2005), ANYL-438. American Chemical Society: Washington, D. C.
CODEN: 69HFCL
DOCUMENT TYPE: Conference; Meeting Abstract; (computer optical disk)
LANGUAGE: English
AB Much attention has been focused on the use of microfluidics to improve cell culture and manipulation by creating biomimetic microenvironments.(1) Cell-based assays in microfluidic systems will also benefit from decreased reagent consumption, smaller cell populations, higher parallelism and automation. However, to take full advantage of microfluidic systems as culture sizes decrease toward single cell assays, it becomes important to accurately control cell placement and attachment. We present here the generation of ordered cell arrays inside microfluidic devices using dielectrophoretic trapping of neural cells. Polyelectrolyte multilayers (PEMs) are used to treat the microfluidic device, rendering it amenable to cellular attachment. It was found that >85% of cells were immobilized as they flowed through the microfluidic device. Using PEM treatment, neural cells remained adherent in a line perpendicular to flow after the electrodes were no longer energized (Figure 1). 1. Beebe, D.;Folch, A. Lab on a Chip 2005, 5, 10-11.

L5 ANSWER 17 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 2004:1124233 CAPLUS
DOCUMENT NUMBER: 142:444260
TITLE: Apoptotic cell death dynamics of HL60 cells studied

using a microfluidic cell trap device
AUTHOR(S): Valero, Ana; Merino, Francisco; Wolbers, Floor; Luttge, Regina; Vermes, Istvan; Andersson, Helene; van den Berg, Albert
CORPORATE SOURCE: BIOS, the Lab-on-a-chip Group, MESA+ Institute for Nanotechnology, University of Twente, Enschede, 7500 AE, Neth.
SOURCE: Lab on a Chip (2005), 5(1), 49-55
CODEN: LCAHAM; ISSN: 1473-0197
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This paper presents the design, fabrication and first results of a microfluidic cell trap device for anal. of apoptosis. The microfluidic silicon-glass chip enables the immobilization of cells and real-time monitoring of the apoptotic process. Induction of apoptosis, either elec. field mediated or chemical induced with tumor necrosis factor (TNF-α), in combination with cycloheximide (CHX), was addressed. Exposure of cells to the appropriate fluorescent dyes, FLICA and PI, allows one to discriminate between viable, apoptotic and necrotic cells. The results showed that the onset of apoptosis and the transitions during the course of the cell death cascade were followed in chemical induced apoptotic HL60 cells. For the case of elec. field mediated cell death, the distinction between apoptotic and necrotic stage was not clear. This paper presents the first results to analyze programmed cell death dynamics using this apoptosis chip and a first step towards an integrated apoptosis chip for high-throughput drug screening on a single cellular level.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 18 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 9
ACCESSION NUMBER: 2004:824715 CAPLUS
DOCUMENT NUMBER: 142:257233
TITLE: Molded polyethylene glycol microstructures for capturing cells within microfluidic channels
AUTHOR(S): Khademhosseini, Ali; Yeh, Judy; Jon, Sangyong; Eng, George; Suh, Kahp Y.; Burdick, Jason A.; Langer, Robert
CORPORATE SOURCE: Division of Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA, 02139, USA
SOURCE: Lab on a Chip (2004), 4(5), 425-430
CODEN: LCAHAM; ISSN: 1473-0197
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The ability to control the deposition and location of adherent and non-adherent cells within microfluidic devices is beneficial for the development of micro-scale bioanal. tools and high-throughput screening systems. Here, the authors introduce a simple technique to fabricate poly(ethylene glycol) (PEG) microstructures within microfluidic channels that can be used to dock cells within pre-defined locations. Microstructures of various shapes were used to capture and shear-protect cells despite medium flow in the channel. Using this approach, PEG microwells were fabricated either with exposed or non-exposed substrates. Proteins and cells adhered within microwells with exposed substrates, while non-exposed substrates prevented protein and cell adhesion (although the cells were captured inside the features). Furthermore, immobilized cells remained viable and were stained for cell surface receptors by sequential flow of antibodies and secondary fluorescent probes. With its unique strengths in utility and control, this approach

is potentially beneficial for the development of cell-based anal. devices and microreactors that enable the capture and real-time anal. of cells within microchannels, irresp. of cell anchorage properties.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 19 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:829023 CAPLUS

TITLE: Nanoliterbioreactor: Monitoring of long-term mammalian cell physiology at nanofabricated scale

AUTHOR(S): Prokop, Ales; Prokop, Zdenka; Schaffer, David; Kozlov, Eugene; Wikswo, John; Cliffel, David; Baudenbacher, Franz

CORPORATE SOURCE: NanoDelivery, Inc., Nashville, TN, 37211, USA

SOURCE: Materials Research Society Symposium Proceedings (2004), 823(Biological and Bioinspired Materials and Devices), 163-174
CODEN: MRSPDH; ISSN: 0272-9172

PUBLISHER: Materials Research Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB There is a need for microminiaturized cell-culture environments, i.e., NanoLiter BioReactors (NBRs), for growing and maintaining populations of up to several hundred cultured mammalian cells in vols. three orders of magnitude smaller than those contained in standard multi-well screening plates. Reduced NBR vols. would not only shorten the time required for diffusive mixing, for achieving thermal equilibrium, and for cells to grow to confluence, but also simplify accurate cell counting, minimize required vols. of expensive anal. pharmaceuticals or toxins, and allow for thousands of culture chambers on a single instrumented chip. These devices would enable the development of a new class of miniature, automated cell-based bioanal. arrays for monitoring the immediate environment of multiple cell lines and assessing the effects of drug or toxin exposure. The challenge, beyond that of optimizing the NBR phys., is to detect cellular response, provide appropriate control signals, and, eventually, facilitate closed-loop adjustments of the environment--e.g., to control temperature, pH, ionic concentration, etc., to maintain homeostasis, or to apply drugs or toxins followed by the adaptive administration of a selective toxin antidote. To characterize in a nonspecific manner the metabolic activity of cells, the biosensor elements of the NBR might include planar pH, dissolved oxygen, and redox potential sensors, or even an isothermal picocalorimeter (pC) to monitor thermodn. response. Equipped with such sensors, the NBR could be used to perform short- and long-term cultivation of several mammalian cell lines in a perfused system, and to monitor their response to analytes in a massively parallel format. This approach will enable automated, parallel, and multiphasic monitoring of multiple cell lines for drug and toxicol. screening. An added bonus is the possibility of studying cell populations with low cell counts whose constituents are completely detached from typical tissue environment, or populations in controlled phys. and chemical gradients. We fabricated NBR prototypes, each of which incorporates a culture chamber, inlet and outlet ports, and connecting microfluidic conduits. The fluidic components were molded in PDMS using soft-lithog. techniques, and sealed via plasma activation against a glass slide, which served as the primary culture substrate in the NBR. The input and outlet ports were punched into the PDMS block, and enabled the supply and withdrawal of culture medium into/from the culture chamber (10-100 nL volume), as well as cell seeding. Prior to implementation, the NBRs were sterilized in a UV-exposure chamber. Medium was introduced using WPI nanoliter injectors actuated with a timer. This system allowed batch, fed-batch, and continuous feed arrangements, as well as in situ

optical and fluorescence microscopy of the culture progress. Because of the intrinsically high oxygen permeability of the PDMS material, no addnl. CO2/air supply was necessary. The developmental process for the NBR typically employed several iterations of the following steps: Conceptual design, mask generation, photolithog., soft lithog., and proof-of-concept culture assay. We have arrive data several intermediate designs. One is termed "circular NBR with a central post (CP-NBR", another, "perfusion (grid) NBR (PG-NBR)", and a third version, "multitrap (cage) NBR (MT-NBR", the last two providing total cell retention. The CP-NBR incorporates an 825 μm diameter culture chamber of 25-40 μm height, fitted with a central post of 275 μm diameter This configuration allows optimum fluid distribution and eliminates dead=zones populated with non-perfused cells. The PG-NBR includes two grids (sieves) across the flow to retain cells. A third inlet is unobstructed and allows cells seeding. The MT-NBR allows dynamic seeding in consecutively arranged capture cells provided with sieves. It is connected by narrow 100 μm channels (also of 40 μm height) to the inlet and outlet ports. The current design has volume of the central culture chamber of CP-NBR is 20 nL. We examined all three feeding protocols, particularly fed-batch and continuous modes. Three cells lines were selected for detailed testing: a fibroblast cell line, CHO cells, and hepatocytes. Prior to the culturing trials, extensive biocompatibility tests were performed on all materials to be employed in the NBR design. These included the glass substrate, PDMS polymer, Si3N4 and SiO2 (potential materials to be used in a hybrid system for pC inclusion), and different coating materials that would serve as extracellular matrix (ECM) components, including collagen, gelatin, fibronectin, and polylysine. We used a fluoresecent PicoGreen. DNA assay to evaluate the viability and proliferation of all three cell lines over extended periods of time in NBRs with a variety of polymers and coatings. The results were compared to those of cell cultures on plain glass substrates. We found that glass is a quite suitable substrate for cell culturing within the NBR environment, although some improvement was noted with the ECM coating. For all three lines in NBRs, viabilities of more than 90% were achieved with a continuous feed protocol To delineate the effect of cell seeding d. on cell viability and survival, we conducted sep. plating expts. using standard culture protocols in well-plate dishes. Again, PicoGreen assays were used to evaluate the extent of cell growth achieve din 1-5 days following the seeding. Low seeding densities resulted in the absence of cell proliferation for some cell lines because of the deficiency of cell-cell and ECM-cell contacts. Such expts. clearly show that there is a minimal (critical) d. needed for some cell lines to achieve a commencement of cell growth. Fibroblasts, for example, require such a min. cell d. to enable cell proliferation. Other cell lines, such as CHO, are capable of developing a colony from a single cell seed. This observation is of great consequence for initiating the cell growth in the NBR environment. It would be worthwhile to examine the use of ECM and growth factors in an NBR environment to improve cell plating efficiency. In summary, an instrumented NanoBioReactor(NBR) will represent a dramatic departure from the standard culture environment. The employment of NBRs for mammalian cell culture opens a new paradigm of cell biol., so far largely neglected in the literature.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 20 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:829119 CAPLUS
DOCUMENT NUMBER: 142:19348
TITLE: NanoLiterBioReactor: Monitoring of long-term mammalian cell physiology at nanofabricated scale
AUTHOR(S): Prokop, Ales; Prokop, Zdenka; Schaffer, David; Kozlov, Eugene; Wikswo, John; Cliffel, David; Baudenbacher,

Franz
CORPORATE SOURCE: NanoDelivery, Inc., Nashville, TN, 37211, USA
SOURCE: Materials Research Society Symposium Proceedings (2004), 820(Nanoengineered Assemblies and Advanced Micro/Nanosystems), 127-138
CODEN: MRSPDH; ISSN: 0272-9172
PUBLISHER: Materials Research Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB There is a need for microminiaturized cell-culture environments, i.e., NanoLiter BioReactors (NBRs), for growing and maintaining populations of up to several hundred cultured mammalian cells in vols. three orders of magnitude smaller than those contained in standard multi-well screening plates. Reduced NBR vols. would not only shorten the time required for diffusive mixing, for achieving thermal equilibrium, and for cells to grow to confluence, but also simplify accurate cell counting, minimize required vols. of expensive anal. pharmaceuticals or toxins, and allow for thousands of culture chambers on a single instrumented chip. These devices would enable the development of a new class of miniature, automated cell-based bioanal. arrays for monitoring the immediate environment of multiple cell lines and assessing the effects of drug or toxin exposure. The challenge, beyond that of optimizing the NBR phys., is to detect cellular response, provide appropriate control signals, and, eventually, facilitate closed-loop adjustments of the environment--e.g., to control temperature, pH, ionic concentration, etc., to maintain homeostasis, or to apply drugs or toxins followed by the adaptive administration of a selective toxin antidote. To characterize in a nonspecific manner the metabolic activity of cells, the biosensor elements of the NBR might include planar pH, dissolved oxygen, and redox potential sensors, or even an isothermal picocalorimeter (pC) to monitor thermodn. response. Equipped with such sensors, the NBR could be used to perform short- and long-term cultivation of several mammalian cell lines in a perfused system, and to monitor their response to analytes in a massively parallel format. This approach will enable automated, parallel, and multiphasic monitoring of multiple cell lines for drug and toxicol. screening. An added bonus is the possibility of studying cell populations with low cell counts whose constituents are completely detached from typical tissue environment, or populations in controlled phys. and chemical gradients. We fabricated NBR prototypes, each of which incorporates a culture chamber, inlet and outlet ports, and connecting microfluidic conduits. The fluidic components were molded in PDMS using soft-lithog. techniques, and sealed via plasma activation against a glass slide, which served as the primary culture substrate in the NBR. The input and outlet ports were punched into the PDMS block, and enabled the supply and withdrawal of culture medium into/from the culture chamber (10-100 nL volume), as well as cell seeding. Prior to implementation, the NBRs were sterilized in a UV-exposure chamber. Medium was introduced using WPI nanoliter injectors actuated with a timer. This system allowed batch, fed-batch, and continuous feed arrangements, as well as in situ optical and fluorescence microscopy of the culture progress. Because of the intrinsically high oxygen permeability of the PDMS material, no addnl. CO2/air supply was necessary. The developmental process for the NBR typically employed several iterations of the following steps: Conceptual design, mask generation, photolithog., soft lithog., and proof-of-concept culture assay. We have arrived at several intermediate designs. One is termed "circular NBR with a central post (CP-NBR)", another, "perfusion (grid) NBR (PG-NBR)", and a third version, "multitrap (cage) NBR (MT-NBR)", the last two providing total cell retention. The CP-NBR incorporates an 825 μm diameter culture chamber of 25-40 μm height, fitted with a central post of 275 μm diameter This configuration allows optimumfluid distribution and eliminates dead-zones populated with non-

perfused cells. The PG-NBR includes two grids (sieves) across the flow to retain cells. A third inlet in unobstructed and allows cells seeding. The MT-NBR allows dynamic seeding in consecutively arranged capture cells provided with sieves. It is connected by narrow 100 μ channels (also of 40 μm height) to the inlet and outlet ports. The current design has volume of the central culture chamber of CP-NBR is 20 nL. We examined all three feeding protocols, particularly fed-batch and continuous modes. Three cells lines were selected for detailed testing: a fibroblast cell line, CHO cells, and hepatocytes. Prior to the culturing trials, extensive biocompatibility tests were performed on all materials to be employed in the NBR design. These included the glass substrate, PDMS polymer, Si3N4 and SiO2 (potential materials to be used in a hybrid system for pC inclusion), and different coating materials that would serve as extracellular matrix (ECM) components, including collagen, gelatin, fibronectin, and polylysine. We used a fluorescent PicoGreen DNA assay to evaluate the viability and proliferation of all three cell lines over extended periods of time in NBRs with a variety of polymers and coatings. The results were compared to those of cell cultures on plain glass substrates. We found that glass is a quite suitable substrate for cell culturing within the NBR environment, although some improvement was noted with the ECM coating. For all three lines in NBRs, viabilities of more than 90% were achieved with a continuous feed protocol. To delineate the effect of cell seeding d. on cell viability and survival, we conducted sep. plating expts. using standard culture protocols in well-plate dishes. Again, PicoGreen assays were used to evaluate the extent of cell growth achieved in 1-5 days following the seeding. Low seeding densities resulted in the absence of cell proliferation for some cell lines because of the deficiency of cell-cell and ECM-cell contacts. Such expts. clearly show that there is a minimal (critical) d. needed for some cell lines to achieve a commencement of cell growth. Fibroblasts, for example, require such a min. cell d. to enable cell proliferation. Other cell lines, such as CHO, are capable of developing a colony from a single cell seed. This observation is of great consequence for initiating the cell growth in the NBR environment. It would be worthwhile to examine the use of ECM and growth factors in an NBR environment to improve cell plating efficiency. In summary, an instrumented NanoBioReactor (NBR) will represent a dramatic departure from the standard culture environment. The employment of NBRs for mammalian cell culture opens a new paradigm of cell biol., so far largely neglected in the literature.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 21 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 10

ACCESSION NUMBER: 2003:410081 CAPLUS
DOCUMENT NUMBER: 140:177409
TITLE: Microfluidic devices for cellomics: a review
AUTHOR(S): Andersson, Helene; van den Berg, Albert
CORPORATE SOURCE: Silex Microsystems AB, Kista, 164 40, Swed.
SOURCE: Sensors and Actuators, B: Chemical (2003), B92(3), 315-325
CODEN: SABCEB; ISSN: 0925-4005
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review of microfluidic devices for cellomics is presented. After a brief description of the historical background of Lab-on-Chip (LOC) devices, different areas are reviewed. Devices for cell sampling are presented, followed by cell trapping and cell sorting devices based upon mech. and elec. principles. Subsequently, a popular type of cell sorters, flow cytometers, is considered, followed by a chapter describing devices for cell treatment: cell

lysis, poration/gene transfection and cell fusion devices. Finally a number of microfluidic devices for cellular studies are reviewed. The large amount of very recent publications treated in this review indicates the rapidly growing interest in this exciting application area of LOC.

REFERENCE COUNT: 95 THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 22 OF 22 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:914244 CAPLUS

DOCUMENT NUMBER: 138:119288

TITLE: A microfluidic bioreactor based on hydrogel-entrapped E. coli: Cell viability, lysis, and intracellular enzyme reactions

AUTHOR(S): Heo, Jinseok; Thomas, K. Joseph; Seong, Gi Hun; Crooks, Richard M.

CORPORATE SOURCE: Department of Chemistry, Texas A&M University, College Station, TX, 77842-3012, USA

SOURCE: Analytical Chemistry (2003), 75(1), 22-26
CODEN: ANCHAM; ISSN: 0003-2700

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Viable E. coli cells were entrapped in hydrogel micropatches photopolymd. within microfluidic systems. The microfluidic channels and the micropatches have sizes on the order of 100-500 μm. Small mols., such as dyes and surfactants, present in the solution surrounding the hydrogel, are able to diffuse into the gel and encounter the cells, but the cells are sufficiently large to be retained. For example, SDS is a lysis agent that is able to penetrate the hydrogel and disrupt the cellular membrane. Entrapment of viable cells within hydrogels, followed by lysis, could provide a convenient means for preparing biocatalysts without the need for enzyme extraction and purification Hydrogel-immobilized cells are able to carry out chemical reactions within microfluidic channels. Specifically, a nonfluorescent dye, BCECF-AM, is able to penetrate both the hydrogel and the bacterial membrane and be converted into a fluorescent form (BCECF) by the interior cellular machinery. These results suggest that cells immobilized within microfluidic channels can act as sensors for small mols. and as bioreactors for carrying out reactions.

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